Mini Review

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Clinical application of presepsin as diagnostic biomarker of infection: overview and updates

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Abstract: The appropriate identification of bacterial infection is the basis for effective treatment and control of infective disease. Among this context, an emerging biomarker of infection is presepsin (PSP), recently described as early marker of different infections. PSP secretion has been shown to be associated with monocyte phagocytosis and plasmatic levels of PSP increase in response to bacterial infection and decrease after antibiotic treatment, therefore it can be considered a marker of activation of immune cell response towards an invading pathogen. Different methods have been developed to measure PSP and this review will briefly describe the different clinical fields of application of PSP, ranging from intensive care to neonatal infection, to orthopedic and pulmonary infection as well as fungal infections and cardiovascular infections.

Keywords: bacterial infection; presepsin; serum marker.

Introduction

Infections are a major problem in clinical practice. The appropriate identification of bacterial infection is the basis for effective treatment and control of infectious diseases [1]. The problem with the recognition of bacterial infections is that clinical presentation by signs and symptoms often overlap with other inflammatory disorders. The current approach for infection diagnosis is based on microbiological culture, biochemical methods and molecular techniques, but, on the one hand, there is still the lack of a gold standard because these approaches still have limits in sensibility and specificity; on the other hand, these biochemical and molecular approaches often need expensive technologies and equipment, not affordable by every analysis laboratory [2]. Therefore, there is the continuous requirement for cost-effective, fast, simple, reliable, specific and sensitive biomarkers for diagnosis of infection.

In this context, an emerging biomarker of infection is presepsin (PSP), recently described as an early marker of different infections [3, 4]. PSP is a fraction of the soluble form of CD14 subtype (sCD14-ST). CD14 belongs to the Toll-like receptor family (TLR), which plays a role in identifying different ligands of both Gram-positive and Gram-negative bacteria and stimulates the inflammatory response. In particular CD14 can exist in two forms: membrane bound (mCD14), expressed on the membrane of monocyte/macrophage cells and the soluble form (sCD14) present in plasma, where is cleaved by cathepsin D into a 13 kDa fragment, called PSP [5].

Plasmatic levels of PSP have been shown become elevated in response to bacterial infection and decrease after antibiotic treatment, therefore it can be considered a marker of activation of immune cell response towards an invading pathogen. PSP secretion has also been shown to be associated with monocyte phagocytosis [6]; therefore PSP could also be measurable in healthy not infected subjects. This reason is crucial in having a specific and sensitive method to measure PSP, in order to associate an increase from the physiological cut-off value to the presence of a bacterial infection, and the amount of this increase to the intensity of the immune response, thus to the severity of the infection.

Different methods have been developed to measure PSP. The first method was a canonical two-step ELISA assay, measuring PSP in a range of 3–150 ng/mL, but it

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lacked accuracy and it was time consuming. Thermo Fisher developed a rapid assay to measure PSP, modifying the ELISA from a two-step method to a one-step method as follows: (a) sample dilution was eliminated; (b) in order to increase the sensitivity, the following two new anti-PSP antibodies were used: F1106-13-3 monoclonal antibody as the capture antibody and S68 polyclonal antibody as the detection antibody; and (c) the standards were changed from recombinant CD14 (S286C) to recombinant PSP. As a result of these changes, the total assay time was decreased from 4 h to 1.5 h, and the dynamic range of the one-step assay was changed to 0.05–3.00 ng/mL (compared to 3–150 ng/mL with the two-step ELISA) [7].

A step forward in the plasmatic measure of PSP is represented by the PATHFAST system (Mitsubishi Chemical), which a novel, highly sensitive and fully automated method, based on chemiluminescence (CLEIA), providing results in 17 min in six samples simultaneously [8]. PATHFAST is a compact immunoanalyzer analysis system for laboratories, hospitals and medical offices available wherever fast quantitative results (with full-scale laboratory quality) are required. The test principle is based on a non-competitive CLEIA combined with MAGTRATION technology (MAGTRATION is technology of bound/free [B/F] separation where magnetic particles are washed in a pipette tip). Magnetic particles were coated by anti-PSP polyclonal antibody and monoclonal antibody. During incubation with plasma, they form immunocomplexes with PSP present in the sample. After incubation, PATHFAST transfers in the new well sample immunocomplexes, with anti-PSP polyclonal and monoclonal antibody coated on magnetic particles bounded with PSP present in the sample. A chemiluminescent substrate (CDP-Star Chemiluminescent Substrate) is added. After a short incubation, the luminescence intensity generated by the enzyme reaction is measured. The luminescence intensity is directly correlated to the PSP concentration in the sample which is calculated by means of the standard curve [9].

Being an emerging and powerful maker of infection and sepsis, measuring PSP have recently reached different clinical fields of application, as shown in Figure 1, ranging from intensive care to fungal infection [10], as described in the following sections of this review and summarized in Table 1.

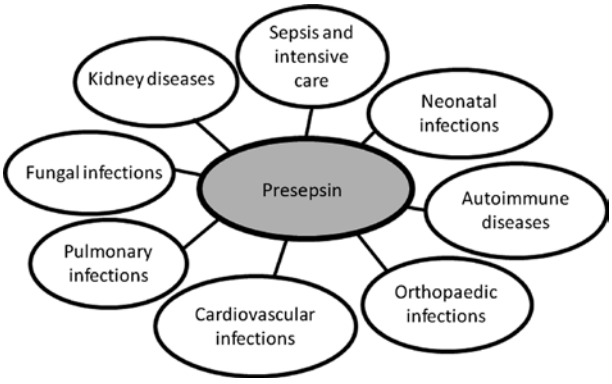

Figure 1: Clinical application of PSP as a marker of infection.

PSP in sepsis and the intensive care and emergency departments

Sepsis was the first clinical context where PSP was evaluated as a biomarker. Sepsis is a major challenge in emergency departments and intensive care units (ICUs), causing high mortality and morbidity [31], therefore an early diagnosis is crucial for a timely intervention in order to improve the prognosis of septic patients [31].

Several multicentric prospective studies evaluated PSP in sepsis [31], showing that the efficiency of PSP depends on the cut-off used: the cut-off of 600 ng/mL, sensitivity

Table 1: Summary of studies about diagnostic and prognostic value of PSP.

Clinical applications of PSP	Diagnostic	Prognostic	References
Sepsis	Yes	Yes	[4, 5]
Intensive care unit and emergency department	Yes	Yes	[11, 12]
Neonatal intensive care	Yes	Yes	[13–15]
Pulmonary infections	Yes	Yes	[16–19]
Autoimmune diseases	Yes	To be defined	[20–22]
Kidney diseases	Yes	To be defined	[23, 24]
Cardiovascular infections	Yes	To be defined	[25–27]
Orthopedic prosthesis infections	Yes	Yes	[3, 28]
Fungal infections	Yes	To be defined	[29, 30]

PSP, presepsin.

and specificity were 70.3% and 81.3%, respectively, while the cut-off of 864 sensitivity increased to 71.4% but specificity decreased to 63.8% [11]. A recent meta-analysis evaluated the diagnostic value of PSP for sepsis, indicating an overall diagnostic sensitivity of 0.83 and specificity of 0.78, with an ROC value of 0.88. The positive and negative likelihood ratios, considered to be more clinically meaningful, were 3.9 and 0.21, respectively [1]. As a positive likelihood ratio is considered clinically acceptable for values higher than 10, PSP cannot be used alone as a marker to rule out sepsis, but should be associated with other sepsis markers, such as procalcitonin (PCT), and to the clinical context confirming the diagnosis of sepsis [1, 12].

PSP in neonatal intensive care and sepsis

Neonatal sepsis is a major cause of morbidity and mortality, especially in preterm infants. As the disease can rapidly progress in septic shock and multiple organ dysfunction, early diagnosis is critical to improve survival. The gold standard for sepsis diagnosis is a blood culture, but it requires at least 48–72 h and it still gives a not negligible number of false negatives, in particular in the early onset sepsis, where the blood culture sensitivity is less than 10% [13]. Traditional biomarkers such as PCT and C-reactive protein (CRP) were inadequate in the accurate prediction of neonatal sepsis [14]; therefore, there is still the need for an optimal neonatal sepsis biomarker. PSP has been recently described as having a higher diagnostic accuracy, in terms of AUC value, than PCT and CRP, resulting in more sensitivity in detecting neonatal sepsis [15] suggesting that PSP could be a better biomarker to be used in high-risk neonatal populations to detect early-onset sepsis. A critical aspect is represented by the reliable reference value in healthy term neonates, in order to have an adequate diagnostic accuracy. PSP has been shown to be unaffected by most of the variables affecting PCT and CRP [32], suggesting that PSP could be used as an effective neonatal sepsis biomarker.

PSP in pulmonary infections

Bacteria are common pathogens of community acquired pneumonia (CAP), but bacterial culture detection from blood and sputum requires several days and gives a not negligible number of false negative results [33]. In this context, plasmatic levels of PSP demonstrated a good diagnostic and prognostic value for bacterial CAP (BCAP) [16], being able to predict ICU mortality in these patients [17]. In the case of active pulmonary tuberculosis (APTB), culture basis diagnosis is not widely available, because *Mycobacterium tuberculosis* culturing requires specific and long-lasting culture conditions. Therefore, an early biomarker for the discrimination between *M. tuberculosis* and other bacteria is critical for an early diagnosis and a prompt adequate therapy. PSP have been recently described to be increased in APTB patients, thus it could be helpful in the initial differential diagnosis between APTB and BCAP. Pneumonia development is also a challenging aspect of the intubated newborn [18], where blood sample collection is critical. In this context, PSP measurement in the tracheal aspirate was recently suggested as a complementary marker in the diagnosis of early onset neonatal pneumonia [19].

PSP in autoimmune disease

Infection is a critical complication of autoimmune diseases, such as rheumatoid arthritis (RA), because the traditional inflammatory markers, such as CRP, are elevated both during infection and the high activity phase of RA, thus they cannot be useful for a differential diagnosis between the two conditions [34]. On the contrary, PSP is affected neither by RA disease activity nor by low-dose corticosteroids and methotrexate used in RA; therefore, it can be an effective diagnostic marker for bacterial infection in RA patients [20]. Special attention should be directed to baseline levels considered in these conditions, because PSP in RA patients are higher than in healthy controls [20]. Conversely, in other autoimmune diseases such a systemic lupus erythematosus (SLE), PSP correlates with the disease activity of SLE [21]. Therefore, the use of PSP as a bacterial infection biomarker cannot be applied to all autoimmune disease but only to those where PSP is not affected itself by the disease activity. To overcome this problem, a recent study associated the measure of PSP in SLE patients to neutrophils CD64 expression and PCT, in order to differentiate infections from activity in SLE patients [22].

PSP in kidney disease

The plasmatic level of PSP is affected by kidney function. As PSP is a 13 kDa protein, it can be filtered by the

glomerulus and re-adsorbed within proximal tubular cells. Therefore, any condition affecting kidney filtrating function reflects on plasmatic PSP values. Recent evidence has shown that PSP increases as the glomerular filtration rate (GFR) decreases, and its plasmatic levels correlates with serum creatinine levels in ICU patients [23]. In patients receiving hemodialysis therapy (HD), PSP displayed high levels, compared with those observed in severe sepsis and septic shock, while in patients not receiving HD, PSP plasmatic levels were negatively correlated with GFR. These results suggest that the evaluation of PSP in patients with chronic kidney disease (CKD) requires a particular caution and the definition of a specific cut-off value for these patients. In critically ill patients, sepsis is the most common cause of acute kidney injury (AKI); therefore, there is the urgent need of a biomarker able to identify sepsis in AKI patients. On the one hand, PSP is elevated in septic conditions, on the other hand high, PSP level are also observed in AKI patients who are not septic and it correlates with AKI severity [24]. This evidence, however, suggests that in patients with severe AKI, the diagnostic accuracy of PSP for sepsis is lower than PCT, and a different threshold should be used for the diagnosis of sepsis when using PCT and PSP in patients with severe AKI.

Measuring PSP in cardiovascular diseases

Prediction of complications and mortality after cardiac surgery is an important aspect of the timely correction of these conditions. One possibility in these cases is the use of biomarkers and some prognostic scores, in order to predict adverse operative complications, such as infections and mortality. A recent longitudinal study monitored PSP levels in patients peri-operatively who operated on for acquired heart diseases with cardiopulmonary bypass (CPB) [25]. Statistically significant differences in PSP levels can be seen using APACHE II (Acute Physiology and Chronic Health Evaluation II) and sequential organ failure assessment (SOFA) scores in groups of patients with and without infection. These results suggested that the use of new generation biomarkers such as PSP alongside integral severity-of-disease scores allows the prediction of the risk of infectious complications and mortality in cardiosurgical patients. Similarly, PSP seems to be as valuable a biomarker as PCT or CRP in the evaluation of infectious complications in patients after heart transplantation [26].

Infections of devices remains a significant challenge as clinical indications for cardiovascular implantable electronic device (CIED) therapy continue to expand beyond the prevention and treatment of cardiac arrhythmias. Patients receiving CIED therapy are now older and have significant co-morbidities, leading to risk of complications, including infection. CIED infection warrants complete device removal, as retention is associated with an unacceptably high risk of relapse and increased mortality. However, accurate diagnosis of CIED infections remains a significant challenge. The use of biomarkers in the diagnosis of CIED infections is recent but continuously improving: significative importance has already been shown for PCT and high senility CRP, and PSP could be a next potential CIED infection biomarker [27].

PSP in prosthetic joint infections (PJI)

Post-operative PJI is the most common cause of failure of total joint arthroplasty, requiring revision surgery, but a gold standard for the diagnosis and the consequent treatment of PJI is still lacking [28, 35] PSP has a greater diagnostic value than CRP and IL-6 in the diagnosis of PJI [28]. In addition, PSP also displayed a good prognostic value along with infection resolution, indicating that PSP can be considered a useful tool for the diagnosis and clinical monitoring of PJI, and it can also be supported by a panel of new inflammatory makers involved in monocyte/macrophage-mediated inflammatory response such as TLR2, OPN, CCL2 and SuPAR [3].

PSP in fungal infections

Invasive fungal infections are a challenging issue gaining increasing attention in the recent years. Recent statistics attest that fungi are responsible for approximately 20% of all sepsis cases, with fatal outcome reaching 80% [29]. For this reason, early and precise diagnosis is critical for establishing a timely and appropriate treatment and to avoid a worse outcome. Mycological testing and blood culture have important limitations that could be overcome by serologic testing emerging as a valuable perspective for diagnosing patients with invasive fungal infections. In this context, a recent study of Lippi and Cervellin indicated that an increase of PSP values combined to little if no alteration of PCT concentration would be suggestive for invasive fungal infection [10]. Similar, Bamba et al. recently showed that plasmatic PSP levels increased

in patients with fungal bloodstream infections, displaying a positive association with the disease severity [30]. Taken together these recent evidences suggest that PSP could be a useful biomarker of sepsis secondary to fungal infections.

Limits of measuring PSP

PSP metabolism and excretion is influenced by kidney function, therefore particular attention is required in the evaluation of PSP in patients with CKD. In particular PSP concentration was higher in patients undergoing hemodialysis, therefore a different cut-off value should be considered for these patients. Some physiological and pathological conditions can influence PSP levels, such as age, in particular in neonates and elderly subjects, as well as steroid usage, bacteremia, burn or hemophagocytic syndrome [36]. Future studies will be necessary to determine the different cut-off values for the detection of different kinds of infections and in different conditions.

Even though PSP can be considered a good marker of a condition of infection, it is not efficient in the identification of the etiology of the infection. Therefore, for the specific identification of the pathogen, a culture-based method is still needed to be applied along with immunologic biomarkers.

In order to be introduced in the clinical practice, PSP must be compared to currently used clinical biomarkers for sepsis and infection, such as PCT and CRP. At the moment there are limited meta-analysis on the diagnostic performance of PSP with these biomarkers [37]. A recent meta-analysis compared PSP with PCT [38] for diagnosis of early stage sepsis in critically ill patients, and concluded that both biomarkers display similar efficacy, suggesting using the two biomarkers in combination. In addition, a study on preterm neonatal sepsis indicated that PSP could be a more independent predictor of sepsis than PCT and CRP in this clinical setting [32]. Similarly, a multicenter prospective study indicated that PSP is more closely associated to the SOFA and APACHE score than PCT in the clinical evaluation of patients in emergency room and ICU [39]. The evaluation of this new biomarker is still at the investigative stage, and there is still a lack of interventional research regarding diagnosis and antibiotic use. To the best of our knowledge, so far only one multicenter randomized trial measured the correlation of decrease of circulating PSP with antibiotic therapy [40], but further investigation in this field and large scale trials are needed before recommending it as a clinical routine.

Another aspect that should be taken onto account is the cost-effectiveness and feasibility of the measure of new biomarkers. So far no extensive studies have evaluated this aspect, but a recent study by Amastha et al. [41] evaluated the cost effectiveness of PSP and cCRP, indicating a similar cost-effectiveness, in the diagnosis of several bacterial infections. Also, in this context, larger scale studies should be performed in order to reach a substantial conclusion.

Conclusions

PSP can be considered a useful tool for early diagnosis and prognosis of different kind of infections. It shows high sensitivity for bacterial infection and its clinical performance is higher than PCT in some clinical conditions, as PSP results from a dose-response mechanism of host-pathogen interaction (phagocytosis). However, as suggested by the recent literature [42] a panel of infection/inflammation biomarkers, according to the kind of infection, in combination with PSP could reinforce the clinical performance and would be more informative. However, larger scale trials evaluating the efficacy and the cost-effectiveness of this marker, compared to currently used biomarkers, would be recommended before introducing PSP in the clinical routine.

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